Local Changes in Rates of Group A Strepococcus Disease and Antibiotic Resistance are Associated with Geographically Widespread Strain Turnover Events

David Metzgar
Erin A McDonough *Anthony W. Hawksworth*
Christian J. Hansen *Patrick J. Blair*
Carl R. Blaesing *Dennis J. Faix*
Darcie Baynes *Kevin L. Russell*

Naval Health Research Center

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Local changes in rates of group A Streptococcus disease and antibiotic resistance are associated with geographically widespread strain turnover events

David Metzgar,[1,*] Erin A. McDonough,[1] Christian J. Hansen,[1] Carl R. Blaesing,[2] Darcie Baynes,[1] Anthony W. Hawksworth,[1] Patrick J. Blair,[1] Dennis J. Faix[1] and Kevin L. Russell[1,3]

[1]Department of Respiratory Diseases Research; Naval Health Research Center; San Diego, CA USA; [2]Preventive Medicine; Naval Hospital Beaufort; Beaufort, SC USA; [3]Global Emerging Infections Surveillance and Response System (GEIS); Armed Forces Health Surveillance Center; Silver Spring, MD USA

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This study addresses the effects of dynamic strain turnover and antibiotic prophylaxis on rates of group A Streptococcus (GAS) antibiotic resistance and disease. The authors analyzed the strain distributions, disease rates and patterns of antibiotic resistance of 802 GAS isolates collected from 2002 through 2007. These samples were collected from patients with GAS infection symptoms at ten military facilities. Macrolide resistance peaked at 25% during 2004, due to the geographically widespread dominance of a single resistant strain (M75). The resistant strain was not retained regardless of local patterns of macrolide use, and resistance rates decreased upon replacement of M75 with macrolide-susceptible strains. Disease rates were similarly correlated with dominance of specific M types. Statistical analysis revealed temporal correlations between strain distributions at multiple locations. Only the most common strains yielded enough data at multiple sites for statistically significant comparison of temporal fluctuations in dominance, but these (including M44, M3, M18, M118 and M6) all yielded highly significant temporal correlations of 90% or greater on yearly scales. As expected given the complexity and variability of strain distributions on shorter time scales, analysis on a monthly scale yielded lower degrees of positive correlation (31–62%), but in this case all significant correlations were still positive. Shifts in antibiotic resistance profiles and disease rates at specific sites appear to be associated with strain replacements happening on larger scales, independent of antibiotic use at individual sites.

Introduction

Populations in crowded conditions for extended periods of time, exemplified by military recruits and deployed troops, are extremely susceptible to contagious acute respiratory disease (ARD).[1-3] The agents most commonly associated with ARD in these situations include group A Streptococcus (GAS), adenovirus and influenza. Vaccines provide excellent protection against adenovirus and influenza while GAS is controlled with antibiotic treatment and/or prophylaxis.[1] When sulfonamide antibiotics were discovered the US military employed them to combat GAS pharyngitis and the severe pneumonias, rheumatic fever, necrotizing fasciitis and other morbidity that can result from invasive GAS infection.[2] This practice was initially effective but within 1 year resistant strains evolved and spread, rendering sulfonamides ineffective.[2] When penicillin was discovered, it too was deployed to decrease the impact of GAS. Penicillin was used prophylactically on entire classes of trainees in order to control both active infections and asymptomatic colonizations that act as reservoirs.[1,4]

The practice of active prophylaxis has continued for over 50 years and remains effective.[1,4,5] Efforts to limit or suspend prophylaxis of US military recruits for periods of more than a few months have often resulted in GAS-associated outbreaks of pharyngitis and ARD.[3,6,7] Penicillin resistance has never arisen in GAS, which may be adaptively incapable of acquiring and/or expressing the most common penicillin resistance factors.[8,9] Between 7 and 30% of recruits are not treated with penicillin due to demonstrated or potential allergies. Some recruit facilities give these individuals other antibiotics, usually macrolides such as erythromycin or azithromycin.[1,10] While untreated subpopulations experience occasional outbreaks of GAS, they are partially protected by prophylaxis of the majority of the population.[1,10,11] This dynamic is similar to that of herd immunity (transmission interference by the proportion of individuals rendered nonsusceptible through preexisting immunity).

*Correspondence to: David Metzgar; Email: davidleemetzgar@yahoo.com
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GAS strains are highly variable in their rate of transmission, antibiotic resistance, range of disease and specific antigenicity.[3,6,7,12-15] GAS is most commonly characterized by serotype and by antibiotic resistance profile. The most common method of direct serological identification is M typing,[16] but this has been widely replaced by inference of M type from *emm* gene sequence analysis,[17] or more indirectly inferred by various forms of multilocus sequence typing.[18] All of these methods have shown broad concordance to the degree that they overlap in coverage.[19]

Analysis of the sample set collected for this study showed very strong correlations between *emm* type and antibiotic resistance phenotypes, as well as strong tendencies for specific types to be associated with outbreaks.[19] Previous studies report similar associations, supporting the temporal and spatial stability of observed correlations. The strong correlation between serotype and phenotype suggests possible clinical uses of rapid genotyping for the inference of antibiotic susceptibility and the prediction of epidemiological and clinical severity.[19]

Turnover between different serotypes is likely driven by cycles of serotype-specific herd immunity in the general population that tend to favor recently rare strains. A larger proportion of the population is susceptible to recently rare types, and hence they are more readily transmitted. Dynamic epidemiology, characterized by rapid turnover between dominant strains, is the recognized pattern for GAS.[20,21] However, the scale on which these turnovers occur has not been well studied. Complete turnover between single dominant strains was seen in a small, somewhat isolated population of children,[21] while less succinct dynamic events were also seen in military recruits.[20] The authors of those studies attributed the turnover events to different factors—herd immunity and close contact in the first case, constant turnover of the population in the second. Here, we observe multiple sites over a period of 6 years to address the potential connection of turnover events on a larger scale and the impact of these events on local changes in antibiotic resistance and virulence.

We present 6 years of GAS surveillance data including site-specific strain distribution time series, GAS disease rate data and temporal patterns of macrolide resistance from ten US military recruit training facilities. We explore the relationship between strain distribution patterns at multiple sites. Finally, the contributions of time, location, prophylaxis regimen and *emm* type to macrolide resistance patterns are discussed.

Results

Molecular epidemiology of GAS among military recruits. Temporal serotype distributions and associated rates of ARD and macrolide resistance are shown in **Figures 1 and 2**, and the legend defining serotype identities and overall distribution is shown in **Figure 3**. The associated patterns of antibiotic use at the studied sites are shown in **Figure 4**.

The simultaneity of specific serotype emergences and turnovers is clear from visual examination. From 2002 through 2004, M75, M6 and M3 were dominant at the two individual sites and in the composite group. These strains became universally less common from 2005 through 2007. They were replaced by M44 and M5 at FLW and MCRD-PI, by M118 at all sites, and by M18 at FLW and in the composite group.

In order to address the significance of these observed correlations we binned data across months and years and tested each *emm* type for temporal correlation of dominance patterns among the two primary sites and the composite group (see **Table 1**). Positive correlations were common and often significant for well-sampled *emm* types, while negative correlations were invariably nonsignificant, supporting our subjective visual interpretation.

Strain turnover and antibiotic resistance. Only a few of the many *emm* types of GAS are responsible for the vast majority of antibiotic resistance. M75 was responsible for 67% of the macrolide resistance observed during the study period despite representing only 10% of the isolates tested for resistance[19] and macrolide resistance did not show any significant temporal and spatial trends independent of the distribution of M75 (see **Figs. 1 and 2**). The specific associations between *emm* type and antibiotic resistance for this sample set has been previously published.[19]

Strain turnover, virulence and rate of GAS pharyngitis. Rate data are superimposed on the serotype distribution graphs (**Fig. 1**) for time periods during which both site population and GAS-associated disease rate were measured. In late 2005 and 2006, there was a marked increase in GAS morbidity among recruits. The noted outbreaks of invasive disease and ARD in 2005–2006 were closely associated with the dominance of M5. The emergence of this apparently virulent and highly transmissible strain, which was associated with many cases of invasive disease and at least two fatalities, preceded a temporary shortage of Bicillin that caused a suspension of prophylaxis at many sites in late 2006.

Discussion

Molecular epidemiology of GAS among military recruits. The data reveal highly dynamic epidemiology, albeit against a more diverse background than seen in smaller and more isolated populations.[21] While it has been suggested that turnovers in military populations simply represent the effect of training class turnover events,[20] the data suggest otherwise. The sites studied here experience constant training class turnover, with approximately 10% of the recruit population being replaced weekly, yet specific *emm* types often dominate specific sites for periods of several months. Different sites often retain different distributions of *emm* types for months at a time, despite constantly receiving recruits from the same general population, suggesting that transmission of specific strains is maintained within sites for periods of several months. For example, M75 is dominant at MCRD-PI while M3 is dominant at FLW from February through May 2004 (see **Fig. 1**).

On the other hand, these two geographically distinct training sites (approximately 500 miles apart) experience many dynamic epidemiological events in parallel. While locally endemic strains may be transmitted within sites on a monthly scale, turnovers on a longer (yearly) scale are likely reflective of widespread strain turnover events that extend across multiple military training sites and possibly the entire general population.

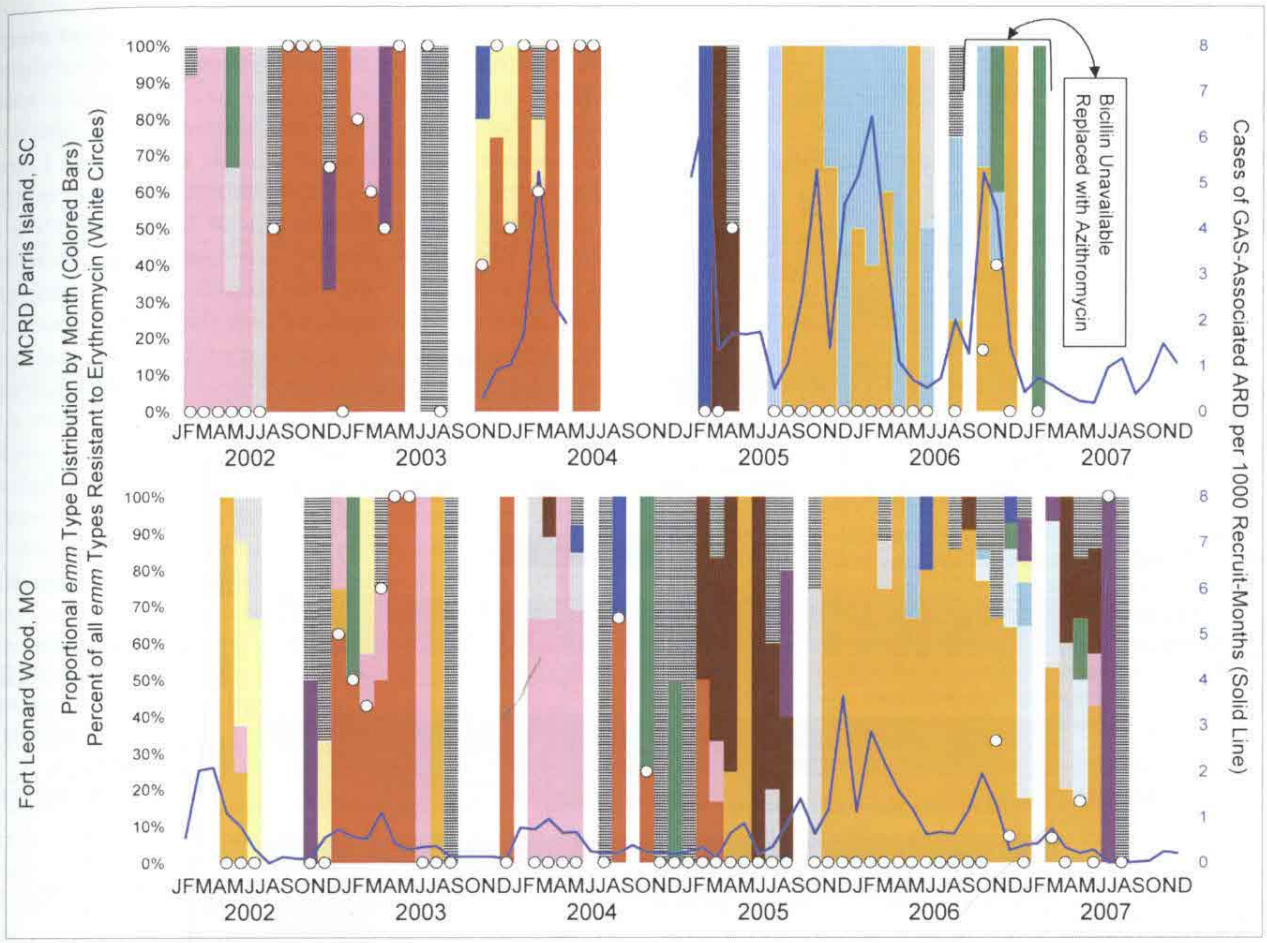

Figure 1. *emm* type distribution, GAS disease rate and erythromycin resistance rate over 6 years at two sites. Temporally aligned *emm* type distributions for two sites that consistently contributed samples. Full names and locations of all sites are given in Acknowledgments. *emm* type color key appears in **Figure 3**.

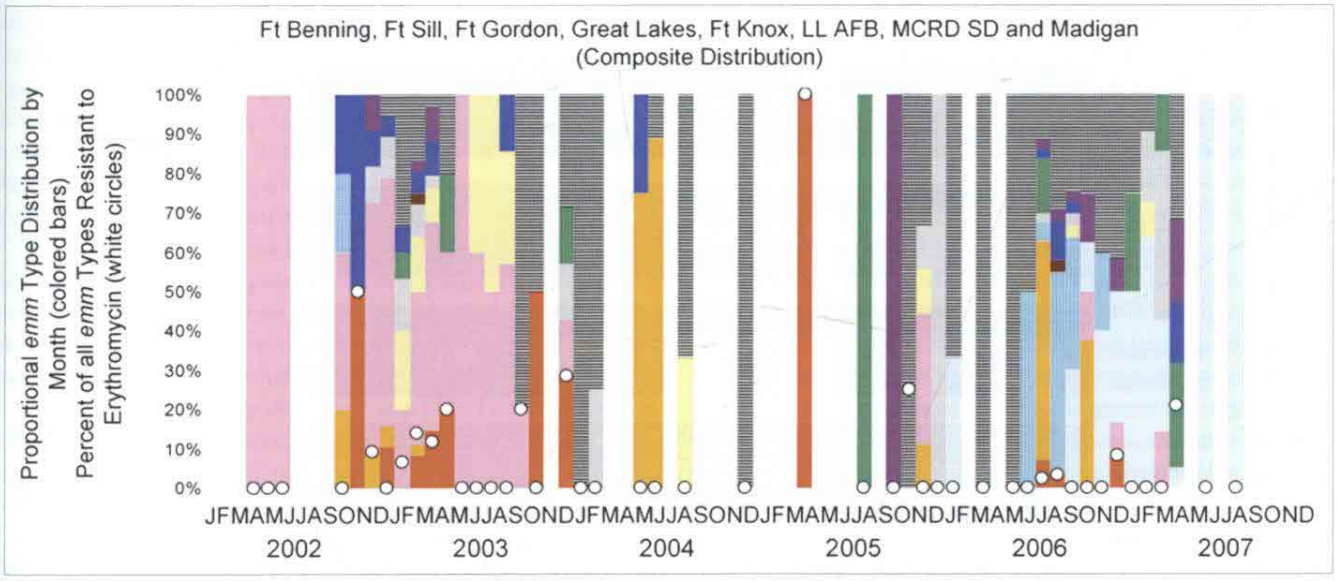

Figure 2. Composite *emm* type distribution and erythromycin resistance rate over 6 years at eight sites. Temporally aligned *emm* type distribution for a composite of eight sites which contributed samples sporadically. Full names and locations of all sites are given in Acknowledgments. *emm* type color key appears in **Figure 3**.

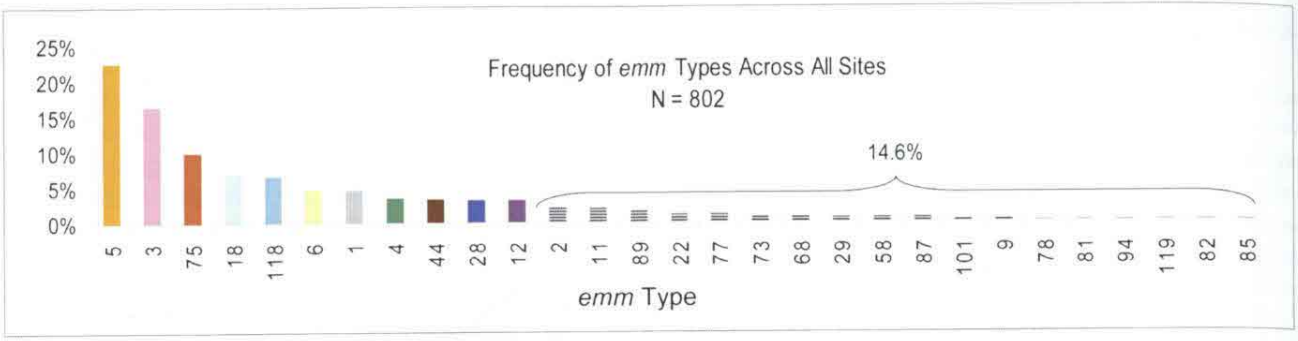

Figure 3. Overall *emm* type distribution at ten sites and key to **Figures 1 and 2.**

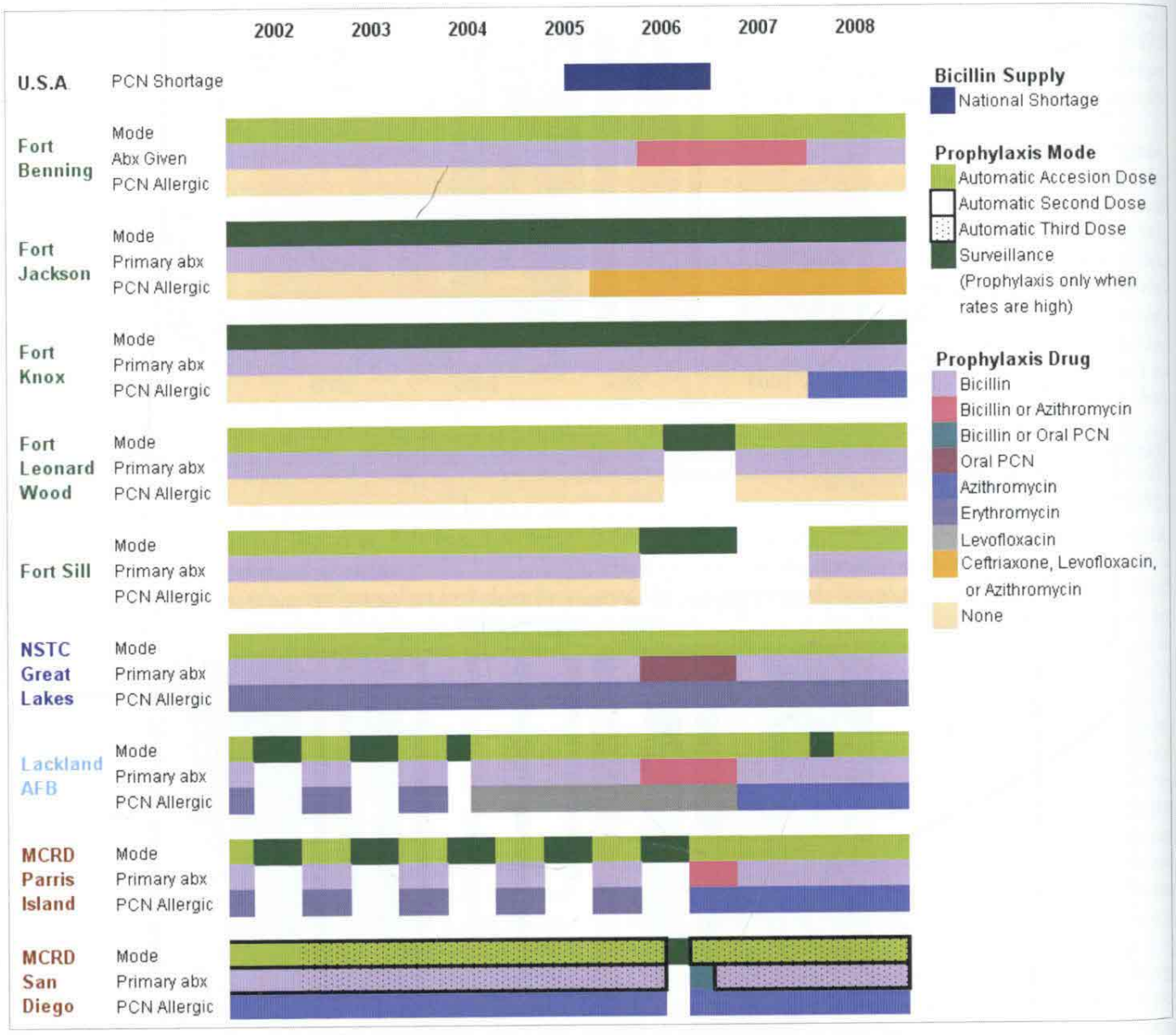

Figure 4. Prophylaxis regimens used to prevent and control GAS outbreaks. Automatic accession dose = prophylaxis upon entry to training. Multidose schedules may vary by site, generally every 3 or 4 weeks. Surveillance indicates sporadic prophylaxis based on observes GAS disease rates. Site names are color coded by service (see Acknowledgments).

Strain turnover and antibiotic resistance. The data support the hypothesis that resistance dynamics result from natural fluctuations in the relative dominance of serotypes that differ in terms of their inherent (and relatively invariable) resistance phenotypes. **Figures 1 and 2** show this clearly, as macrolide resistance can be seen to cycle with the dominance of M75 at all studied sites. This is the opposite of what is seen in many bacteria, such as *Streptococcus pneumoniae*,[22] and provides evidence for relatively strong genetic stability (linkage) in GAS.

FLW used year-round penicillin prophylaxis for all nonallergic recruits but never used macrolides (or other antibiotics) for prophylaxis of penicillin-allergic recruits during the period described in this study. From 1998 through early 2006, MCRD-PI used prophylactic penicillin during the peak GAS season (October 1 through March 31), and during those periods they also used oral macrolides (azithromycin) for penicillin-allergic recruits. Both sites experienced dominance of the primary macrolide-resistant strain M75 in 2002, independent of the fact that one site was actively using macrolides while the other was not. M75 did remain dominant longer at MCRD-PI than at FLW, but use of macrolide prophylaxis did not prevent the subsequent replacement of M75 with macrolide-susceptible strains such as M5, M118 and M44 (see **Fig. 1**).

From October 1, 2006, through March 31, 2007, MCRD-PI used azithromycin prophylaxis for all recruits, due to a national shortage of the Bicillin (penicillin G benzathine) formulation normally used for this purpose. This active use of macrolides was not followed by the emergence or dominance of macrolide-resistant strains, and was not associated with the appearance of new resistance in previously sensitive serotypes.

The pattern of specific antibiotic resistance phenotypes being associated with specific *emm* types held generally true for all *emm* types and all antibiotics,[19] with one exception. The only hospital surveyed in this study (Madigan Army Medical Center) contributed just five isolates, yet these revealed very high rates of erythromycin, tetracycline and clindamycin resistance (see **Table 2**). Furthermore, these isolates were of four different *emm* types, and these *emm* types did not generally display the same resistance patterns in the rest of the sample set. This suggests genetically mobile resistance factors and active selection for resistance are playing a role in the hospital. These phenomena were not evidenced in nonhospital environments[19] (see also **Figs. 1 and 2**).

Strain turnover, virulence and rate of GAS pharyngitis. The data are consistent with previous reports suggesting that only a small number of the known *emm* types are generally associated with high virulence and invasive characteristics, with M1, M3 and M5 foremost among them.[3,6,10,14,15,18,23,24]

In much the same way that the rise and fall of M75 appears responsible for recent spikes in macrolide resistance, the data suggest that the observed spikes in GAS-associated ARD and invasive disease were associated with the shifting dominance of a particularly virulent strain, M5. The association between this serotype and the widespread rate increases seen among trainees from 2002 through 2007 supports the general hypothesis that virulence is strongly linked to serotype. The fact that M5, which did not display any antibiotic resistance phenotypes, was able to cause outbreaks at a site (MCRD-PI) where 70% of the recruits were receiving Bicillin prophylaxis twice during training demonstrates the ongoing threat of GAS to US military trainees. The diverse antibiotic resistance and virulence profiles of different *emm* types necessitate flexible and responsive prophylaxis programs, and demonstrate the potential value of rapid genotyping as a tool for the prediction of clinical and epidemiological severity and for informing treatment and prophylaxis decisions.

Table 1. Significance of temporal correlation of *emm* type frequency between sites

	MCRD Parris Island	Fort Leonard Wood
	By month	**By month**
Fort Leonard Wood	5 (38%; 0.002)	[b]
	75 (31%; 0.01)	[b]
	44 (58%; <0.0001)	[b]
Composite	12 (40%; 0.001)	18 (62%; <0.0001)
		1 (34%; 0.004)
	By year	**By year**
Fort Leonard Wood	44 (97%; 0.002)	[b]
Composite	3 (97%; 0.02)	18 (99%; 0.0003)
	118 (96%; 0.002)	
	6 (91%; 0.01)	

Data shown as "*emm* type (correlation %; Pearson p value)". All significant correlations were positive (distributions changed more synchronously than expected by chance). Nonsignificant correlation values and associated p values are not shown. All *emm* types were analyzed that represented at least 3% of the total isolates (those shown in color in **Fig. 3**). The most heavily sampled *emm* types offered the most positive correlations, suggesting that significance may be limited by sample size for other *emm* types. [b]Blank cells are self comparative.

Materials and Methods

Diagnostic samples were collected by culture on blood agar plates from patients with pharyngitis or other apparent GAS disease. Collection was performed by on-site medical staff as part of routine diagnostic procedures at 10 US military facilities between January 2002 and December 2007 (collection personnel were not members of the author group). Cultured isolates remaining from diagnostic procedures were sent to the Naval Health Research Center with minimal demographic information for purposes of strain typing and antibiotic resistance testing under Naval Health Research Center Institutional Review Board protocol NHRC.2001.0008. Consent was waived because the work was done entirely on deidentified, already existing cultured isolates collected in the process of routing diagnostic testing, and results were not used for diagnosis or patient management. This research has been conducted in compliance with all applicable federal regulations governing the protection of human subjects in research.

Serotyping data from the preceding 5 years of this program, covering many of the same sites, have been described elsewhere.[11] Collection was irregular, being dependent on available time, awareness of and access to apparent cases of GAS disease, and the presence or absence of such disease at any given time.

Table 2. Temporal and geographic distribution of antibiotic resistance phenotypes among group A streptococcus isolates

	Erythromycin		Chloramphenicol		Ofloxacin		Tetracycline		Clindamycin	
Year	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
2002	103	16%	80	3%	80	15%	103	3%	103	1%
2003	171	24%	171	9%	171	15%	171	7%	171	2%
2004	77	25%	77	5%	76	3%	77	7%	77	0%
2005	70	4%	70	19%	70	3%	70	4%	70	0%
2006	271	3%	63	14%	63	0%	271	1%	271	1%
2007	110	7%	0		0		110	2%	110	6%
Site	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
FLW	274	8%	152	11%	151	7%	274	3%	274	0 %
Ft. Benning	31	13%	31	3%	31	13%	31	23%	31	0%
Ft. Sill	85	7%	84	13%	84	11%	85	4%	85	0%
Ft. Gordon	21	0%	0		0		21	0%	21	0%
Great Lakes	92	7%	37	11%	37	11%	92	2%	92	1%
Ft. Knox	39	0%	0		0		39	0%	39	0%
Lackland	44	0%	37	3%	37	19%	44	5%	44	0%
MCRD-PI	140	34%	100	10%	100	6%	140	1%	140	3%
MCRD-SD	71	7%	20	0%	20	5%	71	6%	71	3%
Madigan	5	80%	0		0		5	20%	5	100%

Distribution is shown for all antibiotics to which >1% of the total isolates collected were resistant. N, number tested; %, percent resistant. "Resistance" includes both intermediate and resistant phenotypes per CLSI definitions. Full names and locations of all sites are given in the Acknowledgments section.

Two facilities, Fort Leonard Wood, Missouri (FLW) and Marine Corps Recruit Depot Parris Island, South Carolina (MCRD-PI) consistently provided samples over most of the study period, while other sites submitted samples sporadically. FLW consistently collected both recruit population size (denominator) data and GAS-associated illness (numerator) data, as did MCRD-PI from late 2003 through early 2004 and from 2005 through 2007. This data allowed calculation of GAS-associated illness rates, as depicted in **Figures 1 and 2**.

Positive cultures were resuspended in tryptic soy broth with 15% glycerol, shipped frozen on dry ice to the Naval Health Research Center (NHRC), and stored at -70°C. Traditional *emm* sequencing was employed to type 387 samples. The *emm* types of the remaining 415 isolates were inferred by PCR electrospray ionization mass spectrometry (PCR/ESI-MS) analysis (a rapid form of multilocus genotyping[18]) with reference to correlations between PCR/ESI-MS identity and *emm* sequence identity at the same site during the same year.[19] Antibiotic resistance profiles were generated using standard culture-based inhibition assays as previously described.[19]

In an effort to discern the geographic scale of observed strain turnover events, the temporal patterns of serotype distribution at the two consistently sampled sites were compared with each other and with a third composite group representing less densely sampled sites. Pearson correlation analyses were applied to measure the statistical significance of temporal correlations in dominance of individual *emm* types between pairs of sites on monthly and yearly scales.

General Conclusions

Strain distributions appear to shift in a correlated fashion across multiple sites. This suggests that the observed dynamic epidemiology is reflective of strain turnover events occurring on larger population scales. Macrolide resistance during the study period came primarily from M75, and rates of macrolide resistance were closely correlated with the temporary dominance patterns of M75. The same appears to be true of tetracycline resistance, with almost all resistance coming from 3 *emm* types: M58, M68 and M77[19] (temporal data for tetracycline resistance not shown). Similarly, high rates of GAS-associated ARD and invasive disease were strongly associated with M3 and M5, both of which have previously been associated with high virulence and outbreak potential. We therefore argue that changes in GAS morbidity and mortality, as well as changes in antibiotic resistance rates, are primarily the result of geographically widespread changes in the relative dominance of a few types with unique phenotypes. Antibiotic resistance does not seem to be strongly affected by prophylaxis regimens. Based on this, we argue that *emm* type-specific surveillance could offer a high degree of predictive value related to clinical impact, epidemiological severity and antibiotic resistance. Tracking resistance patterns for the purposes of controlling and understanding the spread of resistance should also be done on an *emm* type-specific basis or any significant trends will be obscured by the indirect effects of strain turnover dynamics.

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Commanding Officer
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140 Sylvester Rd
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Commanding Officer
Naval Medical Research Center
503 Robert Grant Ave
Silver Spring, MD 20910-7500

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14. ABSTRACT (maximum 200 words)

Group A *Streptococcus pyogenes* is a primary agent of respiratory disease in military environments. Antibiotic prophylaxis is used to prevent spread of this pathogen among recruits. We describe effects of dynamic strain turnover and antibiotic prophylaxis on rates of antibiotic resistance and disease through analysis of the temporal and geographic strain distributions, disease rates, and patterns of antibiotic resistance of 802 Streptococcus isolates from 10 US military facilities collected from 2002 through 2007. Most of these sites provided penicillin prophylaxis for all nonallergic recruits, and some sites also used macrolide prophylaxis for penicillin-allergic subpopulations. Macrolide resistance peaked at 25% during 2004, correlating with the geographically widespread dominance of a single strain (M75). The resistant strain was not retained regardless of macrolide prophylaxis, and resistance rates decreased upon replacement of M75. Disease rate was similarly correlated with strain dominance patterns. Temporal correlation in the proportional strain distributions at multiple locations suggest the accompanying shifts in antibiotic resistance profiles may be driven by strain replacements occurring on larger scales. The data suggest that rapid strain-typing methods using sentinel-site samples from a subset of affected locations could offer significant predictive value in terms of both antibiotic susceptibility and potential morbidity patterns.

14. SUBJECT TERMS
GABHS, GAS, serotype, antibiotic resistance, review, epidemiology, strain replacement, military recruit, public health

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